

b. synthesizing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are synthesized without reference to a wild type sequence;

c. introducing a plurality of the nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells; and

f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

4. (Thrice Amended) A method of isolating a functional nucleotide sequence which provides a desired biological activity comprising:

a. providing a means for detecting said desired biological activity;

b. synthesizing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are synthesized without reference to a wild type sequence;

c. introducing a plurality of said nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

- e. expressing said cloning vectors in said host cells;
- f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity; and
- g. isolating said nucleotide sequence or sequences which provide the desired biological activity.

6. (Thrice Amended) A method of isolating a host cell which comprises a functional nucleotide sequence which produces a desired biological activity comprising:

- a. providing a means for detecting said desired biological activity;
- b. synthesizing by enzymatic or chemical synthesis a mixed population of oligonucleotides, wherein said oligonucleotides comprise random sequences, and wherein said random sequences are synthesized without reference to a wild type sequence;
- c. introducing a plurality of said oligonucleotides into a population of cloning vectors to obtain a plurality of cloning vectors containing the oligonucleotides;
- d. introducing said cloning vectors into suitable host cells;
- e. expressing said cloning vectors in said host cells;
- f. screening said host cells to determine whether the inserted oligonucleotide provides the desired biological activity;

g. isolating said host cells having said oligonucleotide having the desired biological activity.

7. (Thrice Amended) A method of producing a mixed population of random nucleotide sequences in order to identify one or more functional sequences which provide a desired biological activity comprising:

a. synthesizing a mixed population of nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids, wherein said nucleotide sequences comprise random sequences; and

b. inserting said mixed population of nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing the nucleotide sequences.

8. (Twice Amended) An isolated, mixed population of vectors comprising nucleotide sequences encoding a mixed population of amino acid sequences, wherein said nucleotide sequences comprise random sequences and have a reduced frequency of stop codons as compared to codons encoding amino acids.

11. (Twice Amended) An isolated, mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences and provide a desired biological activity produced by a method comprising synthesizing the mixed population of nucleotide

sequences in a manner which biases against stop codons, and introducing a plurality of said nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing the nucleotide sequences.

12. (Thrice Amended) A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:
- a. providing a means for detecting said desired biological activity;
  - b. synthesizing a mixed population of nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids, wherein said nucleotide sequences comprise random sequences;
  - c. introducing a plurality of the nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the nucleotide sequences;
  - d. introducing said cloning vectors into suitable host cells;
  - e. expressing said cloning vectors in said host cells; and
  - f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

13. (Thrice Amended) A method of identifying a peptide, polypeptide or protein having a desired biological activity comprising:

- a. providing a means for detecting said desired biological activity;
- b. synthesizing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are synthesized without reference to a wild type sequence;
- c. introducing a plurality of said nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the nucleotide sequences;
- d. introducing said cloning vectors into suitable host cells;
- e. expressing said cloning vectors in said host cells to produce a population of peptides, polypeptides or proteins; and
- f. screening said population of peptides, polypeptides or proteins with said means for detecting the desired biological activity under conditions which allow detection of one or more peptides, polypeptides or proteins from said population having the desired biological activity.

14. (Thrice Amended) A method of identifying a peptide, polypeptide or protein that reacts with a substrate:

- a. providing a substrate;
- b. synthesizing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are synthesized without reference to a wild type sequence;

- c. introducing a plurality of said nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the nucleotide sequences;
- d. introducing said cloning vectors into suitable host cells;
- e. expressing said cloning vectors in said host cells to produce a population of peptides, polypeptides or proteins; and
- f. screening said population of peptides, polypeptides or proteins with said substrate under conditions which allow detection of one or more peptides, polypeptides or proteins from said population that react with said substrate.

15. (Twice Amended) A process for the production of a peptide or protein having a desired biological activity comprising the steps of:

producing by enzymatic or chemical synthesis a random population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said random sequences are produced without reference to a wild type sequence;

forming a library of expression vectors containing the population of nucleotide sequences;

culturing host cells containing the vectors to produce peptides or proteins encoded by the population of nucleotide sequences;

carrying out screening or selection on the host cells, to identify a peptide or protein produced by the host cells having the desired biological function;

isolating a synthesized nucleotide sequence which encodes the identified peptide or protein; and

using the isolated sequence to produce the peptide or protein having the desired biological activity.

16. (Twice Amended) A method of identifying a peptide or protein having a desired biological activity, comprising:

(a) producing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population of nucleotide sequences is produced without reference to a wild type sequence; and

(b) screening said population of peptides or proteins for said desired biological activity under conditions which allow detection of one or more peptides or proteins having said desired biological activity.

17. (Twice Amended) A method of producing a peptide or protein having a desired biological function, comprising:

(a) producing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

(b) screening said population of peptides or proteins for said desired biological function under conditions which allow detection of one or more peptides, polypeptides or proteins having said desired biological function;

(c) isolating the nucleotide sequence(s) encoding said one or more peptides or proteins having said desired biological property; and

(d) producing said peptide or protein.

18. (Twice Amended) A method of producing a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is for use in screening for a desired biological function, comprising adding said nucleotide sequences to an expression vector without reference to a wild type sequence.

19. (Twice Amended) A method of generating a product of an enzyme-substrate reaction, comprising combining a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur, and incubating said population of peptides or proteins with said substrate such that said product may be detected.



20. (Twice Amended) A method of identifying a population of peptides or proteins which catalyze an enzyme substrate reaction, comprising:

- (a) combining a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur;
- (b) incubating said population of peptides or proteins with said enzyme substrate so that a product of said enzyme-substrate reaction may be generated; and
- (c) screening for the product of the enzyme-substrate reaction to identify a population of peptides or proteins which catalyze said enzyme-substrate reaction.

21. (Twice Amended) A process for the production of an expression vector capable of transcribing or translating an open reading frame to produce a desired biological function, said vector comprising a nucleotide sequence, wherein said nucleotide sequence comprises a random sequence, wherein said process comprises the steps of:

producing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

ligating said mixed population of nucleotide sequences into an expression vector to form a library of expression vectors;

transforming suitable host cells with said library of expression vectors;  
growing the transformed host cells containing said expression vectors;  
screening said transformed host cells in order to identify an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function, or selecting said host cells containing an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function;  
isolating the identified or selected transformed host cell; and  
isolating the expression vector from said isolated host cell.

22. (Twice Amended) A method for producing a heterogenous population of vectors comprising:

(a) synthesizing a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said mixed population of nucleotide sequences comprises about a billion or more different nucleotide sequences, said method consisting of random ligation of oligonucleotides or random addition of nucleotide triphosphates without reference to a wild type sequence, and

(b) inserting said heterogenous mixed population of nucleotide sequences into a population of vectors to form a heterogenous population of vectors.

23. (Twice Amended) A process for the production of a nucleotide sequence comprising,

producing by enzymatic or chemical synthesis a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is produced without reference to a wild type sequence;

inserting said population of nucleotide sequences into vectors to form a population of vectors;

introducing said population of vectors into host cells in a manner to produce a population of transformed host cells;

growing independent colonies from the transformed host cells;

screening and/or selecting said colonies of the host cells to identify host cells comprising a nucleotide sequence having a desired biological activity; and

isolating said nucleotide sequence from the selected or screened host cells.

24. (Twice Amended) A method of identifying a nucleotide sequence having a desired biological activity, comprising:

(a) producing by enzymatic or chemical synthesis a mixed population of about a billion or more different nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is produced without reference to a wild type sequence;

(b) screening said population of nucleotide sequences for said desired biological activity under conditions which allow detection of nucleotide sequences having said desired biological activity.

25. (Twice Amended) A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

- a. providing a means for detecting said desired biological activity;
- b. producing by enzymatic or chemical synthesis a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is produced without reference to a wild type sequence;
- c. inserting said population of nucleotide sequences into vectors to form a population of vectors;
- d. introducing said cloning vectors into suitable host cells;
- e. expressing said cloning vectors in said host cells; and
- f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

26. (Amended) A method of producing a host cell which provides a desired biological activity comprising:

- a. producing by enzymatic or chemical synthesis a heterogenous mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein said population is produced without reference to a wild type sequence;
- b. inserting said population of nucleotide sequences into vectors to form a population of vectors; and
- c. transforming a competent host cell with one of said vectors.

27. (Amended) A method of producing a host cell which provides a desired biological activity comprising:

- a. synthesizing using terminal transferase a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise random sequences, and wherein the frequency of stop codons is reduced in comparison to codons encoding amino acids;
- b. making said single-stranded sequences double-stranded using DNA polymerase;
- c. producing a mixed population of vectors containing said nucleotide sequences; and
- d. transforming a competent host cell with one of said vectors.

Please add the following new claims:

28. (New) A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

- a. providing a means for detecting said desired biological activity;

b. synthesizing by enzymatic or chemical synthesis a mixed population of nucleotide sequences, wherein said nucleotide sequences comprise an oligonucleotide consisting of a 5' randomized, a central preselected sequence and a 3' randomized sequence, and wherein said randomized sequences are synthesized without reference to a wild type sequence;

c. introducing a plurality of the nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing the nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells; and

f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.